Menopausal Hormone Therapy and Ovarian Cancer Risk in the National Institutes of Health–AARP Diet and Health Study Cohort

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Background: **Recent studies offer conflicting data on risks of ovarian cancer in users of menopausal hormone therapy. Some findings of increased risks associated with unopposed estrogen use are based on older studies of women with intact uteri, and small sample size and incomplete exposure information have limited the data on estrogen plus progestin associations.** ***Methods:*** **The National Institutes of Health–AARP Diet and Health Study Cohort included 97 638 women aged 50–71 years at baseline who completed two questionnaires (1995–1996 and 1996–1997). We identified 214 incident ovarian cancers among these women through the year 2000 using data from state cancer registries and mortality indexes. We estimated relative risks (RRs) of ovarian cancer for detailed hormone therapy exposures using multivariable proportional hazards regression models. All statistical tests were two-sided.** ***Results:*** **Use of unopposed estrogen for fewer than 10 years was not associated with ovarian cancer. Compared with use of no hormone therapy, use of unopposed estrogen for 10 or more years was statistically significantly associated with ovarian cancer among all women (RR = 1.89, 95% confidence interval [CI] = 1.22 to 2.95; *P* = .004; 56 versus 72 ovarian cancers per 100 000 person-years, respectively) and, albeit not statistically significantly, among women with hysterectomy (n = 19 359, RR = 1.70, 95% CI = 0.87 to 3.31; *P* = .06). Among the 73 483 women with intact uteri, 51 698 had used no hormone therapy or only estrogen plus progestin. Compared with no hormone therapy use, 5 or more years of use of sequential (progestin for <15 days per cycle; RR = 3.09, 95% CI = 1.68 to 5.68; *P*<.001; 49 versus 108 per 100 000 person-years) or continuous (progestin for ≥15 days per cycle; RR = 1.82, 95% CI = 1.03 to 3.23; *P* = .02; 49 versus 66 per 100 000 person-years) estrogen plus progestin regimens were statistically significantly associated with ovarian cancer.** ***Conclusions:*** **Long durations of use of unopposed estrogen and of estrogen plus progestin, especially sequential regimens, are associated with increased ovarian cancer risk. These data expand the range of possible risks associated with menopausal hormone therapy. [J Natl Cancer Inst 2006;98:1397–405]**

Data from early studies *(1–4)* show no association between menopausal hormone therapy and ovarian cancer, but recent studies *(5–11)* suggest that long-duration use of unopposed estrogen is associated with increased ovarian cancer risk. Methodologic issues, such as small sample size or residual confounding by oral contraceptives or hysterectomy *(12)*, might contribute to the discrepancy. However, other recent large studies without obvious limitations *(13,14)* found no associations between ovarian cancer and hormone therapy.

Many of the reports of higher ovarian cancer risks in women who used hormone therapy arose from study populations in which women with intact uteri had used unopposed estrogen *(5–7,9–11)*. This exposure combination, although etiologically and historically intriguing, is of less relevance today because, since the early 1990s, clinical guidelines *(15–17)* have recommended use of estrogen plus progestin formulations for women with intact uteri and use of unopposed estrogen formulations for women with hysterectomy. Data on ovarian cancer risk associated with use according to those guidelines are sparse. Long-duration unopposed estrogen use among women with hysterectomy was associated with statistically significantly increased ovarian cancer risk in two studies *(5,7)*, statistically nonsignificantly increased risk in another *(14)*, and no increased risk in a fourth *(13)*.

Much of the limited data on exposure to estrogen plus progestin and risk of ovarian cancer came from studies of women who previously used unopposed estrogen *(11,14)* or from studies that did not evaluate individual estrogen plus progestin regimens *(10,13,14)*. In one Swedish case–control study *(7)*, use of sequential estrogen plus progestin regimens (i.e., daily estrogen and progestin taken for ≤15 days per cycle) was associated with increased ovarian cancer risk but use of continuous regimens (i.e., daily estrogen and progestin taken for ≥19 days per cycle) was not. Menopausal hormone therapies used in Sweden contain different estrogens and progestins than those used in the United States *(7)*. The difference in formulations may be particularly important for ovarian cancer risk *(18)*. The most detailed US data on continuous combined estrogen plus progestin come from the Women's Health Initiative (WHI), a randomized clinical trial in which this regimen was associated with a statistically nonsignificantly increased ovarian cancer risk, based on 32 participants who developed ovarian cancer *(19)*.

The studies to date do not provide clear evidence on ovarian cancer risk associated with the common patterns of menopausal hormone use in the United States since the early 1990s. Studies with sufficient sample size and exposure details to evaluate specific formulations, regimens, and durations of use are needed to address these questions. Toward that end, we analyzed data from

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the National Institutes of Health (NIH)–AARP Diet and Health Study, a large prospective study of US women.

Subjects and Methods

Study Population

As previously described *(20)*, the NIH– AARP Diet and Health Study was established in 1995–1996 when a baseline questionnaire *(21)* eliciting information on demographic characteristics, dietary intake, and numerous health-related behaviors was mailed to 3.5 million AARP members. Recipients included members between 50 and 71 years of age who resided in one of six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two metropolitan areas (Atlanta, GA, and Detroit, MI). A total of 617 119 persons (17.6%) returned the questionnaire, among whom 566 407 persons (16.2%) satisfactorily completed it. In 1996–1997, we sent a second questionnaire to collect additional information on diet, family history of cancer, anthropometry, physical activity, and use of menopausal hormone therapy. A total of 337 076 respondents (59.5%) completed this questionnaire. After excluding participants who died (n = 1619) or moved out of the study area (n = 547) before their completed second questionnaires were received and scanned, proxy respondents to the baseline questionnaire (n = 6959) or second questionnaire (n = 3424), and all 188 118 men, the study population included 136 409 potentially eligible women.

Exposure Ascertainment

The baseline questionnaire asked whether women were currently taking "replacement hormones," and, if so, for how many years. Participants also reported whether they had had a hysterectomy or oophorectomy. Other characteristics, such as demographics, reproductive history, oral contraceptive use, menopausal status, family history of cancer, and smoking, were included in the baseline questionnaire.

The second questionnaire collected detailed data on use of hormone therapy, including ever use of different preparations and formulations. Estrogen or progestin pill users were asked to report dates of first and last use, total duration of use, regimen, usual dose, and name of the pill that they took for the longest period of time. The questionnaire did not ask about the continuous combined estrogen plus progestin pill, which was first marketed in 1995 *(22)*, but instead asked separately about estrogen and progestin use. The second questionnaire did not update hysterectomy or oophorectomy status.

We considered women who reported taking both estrogen and progestin pills to have used only estrogen plus progestin if the reported dates of first use were within 90 days of each other or if the reported durations of use were identical. We created separate exposure categories for estrogen plus progestin use after use of unopposed estrogen (n = 3964; 4.1%) or unopposed progestin (n = 306; 0.3%), estrogen plus progestin use followed by use of unopposed estrogen (n = 1083; 1.1%) or unopposed progestin (n = 191; 0.2%), use of unopposed estrogen followed by use of unopposed progestin (n = 260; 0.3%), and use of unopposed progestin followed by use of unopposed estrogen (n = 347; 0.4%).

Sequential regimens included estrogen plus progestin use for fewer than 15 days per cycle. Continuous estrogen plus progestin regimens included estrogen plus progestin use every day of the cycle. The 2446 women (3.3% of women without hysterectomy) who reported taking progestin for 15–19 or 20–25 days per cycle were categorized as having used the continuous regimen.

Cohort Follow-up

Study follow-up occurred via two annual linkages. For address changes, the cohort was matched to the National Change of Address database (maintained by the US Postal Service) and also updated based on undeliverable mail, other address change update services, and participants' notifications. For vital status, the Social Security Administration Death Master File identified cohort members who are presumed deceased. A follow-up search of the National Death Index Plus provided verification.

Incident Cancers

A probabilistic linkage to eight state cancer registries, using names, address history, sex, date of birth, and Social Security Number provided on the baseline questionnaire, identified incident cancers. All suspected matches underwent review to reject the potential matches that were unlikely to be true (an estimated 4%), and uncertain matches underwent final manual review. An earlier validation study that compared registry findings with self-reports and medical records estimated that linkage validly identified approximately 90% of all incident cancers *(23)*. The North American Association of Central Cancer Registries certifies all eight registries, which are estimated to be 95% complete for cancers reported up to 24 months prior *(23)*. Date and cause of death from the National Death Index linkage also identified fatal cancers. The Special Studies Institutional Review Board of the US National Cancer Institute approved this study. All participants provided written informed consent.

Analytic Population

To use the detailed hormone therapy data, we restricted analyses to the 136 409 women who completed the second questionnaire. We excluded 9039 women who reported a personal history of cancer other than nonmelanoma skin cancer on either questionnaire (including 398 ovarian cancers), 27 602 who reported a bilateral oophorectomy before baseline, and 2118 whose oophorectomy status was unknown at baseline. We also excluded 12 women who developed nonepithelial ovarian cancer during follow-up. Analysis therefore included 97 638 women.

Through December 31, 2000, 214 women developed epithelial ovarian cancer: 155 in women with intact uteri and 59 in women with hysterectomy. Registry data provided diagnosis dates. Ninety-six cancers were serous, 9 were mucinous, 18 were endometrioid, 16 were papillary, 9 were clear cell, 40 were other adenocarcinomas, and 26 were unclassified histologic types.

Statistical Analysis

We used Cox proportional hazards regression (using SAS 8.2 software, SAS Institute, Inc, Cary, NC), with age as the time scale and ties handled by complete enumeration *(24)*, to calculate hazard ratios and estimate the relative risk (RR) of developing ovarian cancer. Tests of the proportional hazards assumptions for exposures and other variables included in statistical models revealed no departures. Follow-up began at the age at which the second questionnaire was received and scanned. Follow-up ended

on December 31, 2000 (n = 91 958; 94.2%), or the earliest of the following dates: participant was diagnosed with ovarian cancer (n = 214; 0.2%), moved out of her registry catchment area (n = 3218; 2.2%), or died from any cause (n = 2248; 2.3%).

Most women who use unopposed estrogens today have had hysterectomy. However, older women with intact uteri likely had opportunities to take unopposed estrogen before adding progestins became routine for such women *(22)*. We therefore analyzed unopposed estrogen therapy associations both in the entire cohort and in the 19 359 women with hysterectomy at baseline who never used hormones (n = 6335) or only used unopposed estrogen (n = 13 024). The other 4363 women with hysterectomy at baseline reported use of other or unknown hormone therapy formulations. None of the 433 women with unknown hysterectomy status developed ovarian cancer.

We limited the assessment of estrogen plus progestin associations to the 73 483 women with intact uteri at baseline and further restricted analyses to women who never used hormones (n = 38 005) or only used estrogen plus progestin (n = 20 850). In a priori subgroup analyses, we further excluded estrogen plus progestin–only users whose regimen and dose combinations were unknown (n = 767) or differed from historical prescribing patterns in the United States *(16)*: 1) sequential estrogen plus progestin with a progestin dose of less than 1.0 mg/day or 2.5 mg/day (n = 1881), unknown (n = 1351), or "other" (n = 64); 2) continuous estrogen plus progestin with a progestin dose of less than 1.0 mg/day (n = 431), 10.0 mg/day (n = 227), unknown (n = 1931), or "other" (n = 146); or 3) other regimens (n = 359).

We based our detailed hormone therapy variables on the close-ended response categories from the second questionnaire. For both estrogen and progestin, this questionnaire asked women to report total duration of use in 1-year increments up to 10 years and grouped all use greater than 10 years into a single exposure category. All regression models used women who reported no hormone therapy use as the referent group. The models that evaluated more than one hormone therapy formulation or regimen relied on mutually exclusive exposure categories. To assess combinations of exposures (e.g., recency and duration, regimen and recency, or regimen and duration), we created single variables based on cross-tabulations of the two original variables, collapsing cells with small sample sizes as necessary. The statistical models evaluated each exposure class separately, except for estrogen plus progestin regimen; all regimen-specific relative risks were obtained from models that included terms for both regimens.

We initially evaluated potential confounding by all available factors but ultimately chose a parsimonious combination of variables that were associated with both exposure and outcome and changed the hormone therapy parameter estimates compared with estimates from models adjusted for only age at entry. Our statistical models adjusted for continuous age at entry (years) and race/ethnicity (white versus other/unknown), duration of oral contraceptive use (none, <10 years, ≥10 years), menopausal status (premenopausal, postmenopausal, or unknown), and body mass index (BMI; kg/m^2; <25, 25–29, ≥30, or unknown). Analyses of the entire cohort also adjusted for hysterectomy and menopausal status (premenopausal, natural menopause, surgical menopause, or unknown). Analyses of unopposed estrogen in women with hysterectomy were not adjusted for menopausal status because only six women with hysterectomy (none of whom developed ovarian cancer) were premenopausal. Analyses of estrogen plus progestin only in women with intact uteri were adjusted for menopausal status (premenopausal, postmenopausal, or unknown). Additional adjustment for calendar time or other factors (e.g., parity or family history of cancer) did not change the results. Two-sided *P* values were calculated using Wald chi-square tests of categorical (ever use) or ordinal (recency and duration) variables, in which no hormone therapy use was the referent; $P<.05$ was considered statistically significant.

A woman's current age can influence whether she is prescribed sequential or continuous estrogen plus progestin regimens *(16)*. We therefore conducted sensitivity analyses of associations between ovarian cancer and estrogen plus progestin regimens by stratifying regression models by age group at entry.

Results

Characteristics of the Cohort

The 97 638 women accrued 386 468 total person-years. The mean durations of follow-up in women who developed ovarian cancer and women who did not develop ovarian cancer during follow-up were 2.0 years (range = 1 day–4.1 years) and 4.0 years (range = 1 day–4.2 years), respectively. Two women were diagnosed with ovarian cancer and 61 women were censored within 1 month of entry. The mean ± standard deviation ages at entry and exit were 62.5 ± 5.4 years and 66.4 ± 5.4 years, respectively. The standardized incidence ratio for ovarian cancer in the full cohort compared with National Cancer Institute's Surveillance, Epidemiology, and End Results rates (ages 50–79 years) was 0.94 (95% confidence interval [CI] = 0.83 to 1.06).

Most women in the cohort were white, postmenopausal, and in their 60s when they completed the second questionnaire. Women who were overweight (BMI = 25–29 kg/m^2) or obese (BMI ≥ 30 kg/m^2) at baseline contributed just more than half of the total person-time. Overall, ovarian cancer was positively associated with family history of breast cancer; inversely associated with oral contraceptive use, parity, and non-Caucasian race/ethnicity; and not associated with BMI, smoking, age at menarche, or age at natural menopause (Table 1).

Compared with women who never used hormone therapy, women who had used hormone therapy were more likely to be white, to be married, to have used oral contraceptives, to have formerly smoked, and to have a BMI below 25 kg/m^2; women who had used unopposed estrogen were more likely to be postmenopausal, to have had a hysterectomy, and to have given birth at younger ages; and women who had used estrogen plus progestin were more likely to be younger, to have graduated from college, and to have reported excellent or very good overall health (versus good, fair, or poor health) at baseline. Other ovarian cancer risk factors did not differ by duration of unopposed estrogen use or by estrogen plus progestin regimen (data not shown).

Unopposed Estrogen Therapy

In analyses that included all 97 638 participants, women who ever or currently used unopposed estrogen had statistically nonsignificantly increased ovarian cancer risks compared with women who never used hormone therapy (Table 2). Compared with women who never used hormone therapy, women who had used unopposed estrogen for long durations (10 or more years)—most of whom were also current users—had a statistically

Table 1. Associations between risk factors and ovarian cancer among 97 638 women enrolled in the National Institutes of Health–AARP Diet and Health Study Cohort*

Characteristic	No. of cancers	Person-years	RR (95% CI)	P†
Age at study entry, y				
<57	32	76 572		
57–60	29	75 192		
61–64	53	87 012		
65–68	66	97 966		
≥69	34	49 726		
Race/ethnicity				
Caucasian	204	352 766	1.00 (referent)	
Other	10	33 702	0.50 (0.27 to 0.95)	.04
Menopausal status at baseline				
Premenopausal	4	17 608	0.55 (0.19 to 1.61)	
Natural menopause before age 45 y	12	30 969	0.65 (0.36 to 1.20)	
Natural menopause, ages 45–49 y	41	73 627	0.97 (0.66 to 1.42)	
Natural menopause, ages 50–54 y	77	133 031	1.00 (referent)	
Natural menopause, ages ≥55 y	17	30 101	0.95 (0.56 to 1.61)	.32
Surgical menopause	54	89 632	1.07 (0.75 to 1.51)	
BMI at baseline, kg/m^2				
<25	98	175 015	1.00 (referent)	
25–29	63	119 830	0.93 (0.68 to 1.28)	
≥30	43	81 273	1.07 (0.68 to 1.39)	.07
Duration of oral contraceptive use, y				
None	142	228 333	1.00 (referent)	
<10	56	116 911	0.89 (0.64 to 1.23)	
≥10	14	38 783	0.66 (0.38 to 1.14)	.13
Smoking				
Never	109	174 682	1.00 (referent)	
Former	75	156 486	0.77 (0.57 to 1.30)	
Current	26	51 618	0.82 (0.53 to 1.26)	.15
Parity				
Nulliparous	43	60 043	1.00 (referent)	
One	27	38 787	1.01 (0.65 to 1.65)	
Two	61	99 932	0.86 (0.60 to 1.29)	
Three or more	82	186 391	0.57 (0.44 to 0.90)	.001
Age at menarche, y				
≤12	98	186 506	1.00 (referent)	
13–14	99	163 541	1.12 (0.85 to 1.49)	
≥15	17	33 341	0.90 (0.54 to 1.51)	.99
Family history of breast cancer				
No	150	277 272	1.00 (referent)	
Yes	34	47 493	1.29 (0.89 to 1.88)	.18

*Relative risks (RRs) were adjusted for continuous age (years), race (white, other/unknown), menopausal status (premenopausal, postmenopausal, or unknown), duration of oral contraceptive use (none, <10 years, ≥10 years), and body mass index (BMI) (<25, 25–29, ≥30 kg/m^2, or unknown). Not shown are unknown menopausal status (nine cancers and 7792 person-years), BMI (10 cancers and 10 350 person-years), hysterectomy status (1719 person-years), duration of oral contraceptive use (two cancers and 2442 person-years), smoking status (four cancers and 3682 person-years), parity (one cancer and 1315 person-years), age at menarche (1080 person-years), or family history of cancer (30 cancers and 61 703 person-years). CI = confidence interval; BMI = body mass index.

†*P* values (two-sided) were calculated using Wald chi-square tests of ordinal variables based on the categories and reference groups shown. The *P* value for age at menopause was calculated using a Wald chi-square test for an ordinal variable for increasing age at natural menopause (<45, 45–49, 50–54, ≥55 years).

significantly increased risk of ovarian cancer (RR = 1.89, 95% CI = 1.22 to 2.95; *P* = .004; 56 versus 72 ovarian cancers per 100 000 person-years, respectively).

Among women with hysterectomy, the associations between ovarian cancer and unopposed estrogen use were slightly attenuated. All 26 long-duration users who developed ovarian cancer had had a hysterectomy. Compared with never use of hormone therapy, the relative risks associated with long-duration and current long-duration unopposed estrogen use were 1.70 (95% CI = 0.87 to 3.31) and 1.71 (95% CI = 0.87 to 3.35), respectively.

Most of the reported unopposed estrogen use was 0.625 mg of Premarin (conjugated equine estrogens) each day of the cycle. Among women who did not report daily estrogen use, 93% reported taking estrogen at least 20 days per cycle. Approximately 4% and 7% of users of unopposed estrogens reported usually taking lower (0.3 mg/day) and higher (1.25 mg/day) doses, respectively.

Estrogen Plus Progestin in Women With Intact Uteri

Compared with women with intact uteri who never used hormone therapy, women with intact uteri who used only estrogen plus progestin had a statistically significantly increased risk of ovarian cancer (RR = 1.50, 95% CI = 1.03 to 2.19; *P* = .04; Table 3). Risks in women who used unopposed estrogen or unopposed estrogen followed by estrogen plus progestin were elevated, but the increases were not statistically significant. Too few women in these exposure categories developed ovarian cancer to further explore these combinations.

Compared with women with intact uteri who never used hormone therapy, women who used estrogen plus progestin for fewer than 10 years did not have an increased risk of ovarian cancer. Women who used estrogen plus progestin for 10 or more years had statistically significantly increased risks. For users of estrogen plus progestin, as for users of unopposed estrogen, former users and short-duration current users did not

Table 2. Associations between unopposed estrogen therapy–only use and ovarian cancer among women enrolled in the National Institutes of Health–AARP Diet and Health Study Cohort*

Exposure	All women (N = 97 638)				Women with hysterectomy (N = 19 359)			
	No. of cancers	Person-years	RR† (95% CI)	P‡	No. of cancers	Person-years	RR§ (95% CI)	P‡
No HT use	87	176 376	1.00 (referent)		14	25 030	1.00 (referent)	
Only ET	49	71 815	1.33 (0.89 to 2.00)	.17	37	51 455	1.23 (0.67 to 2.27)	.43
Recency of use								
Former	14	23 539	1.15 (0.65 to 2.05)		6	10 355	1.03 (0.40 to 2.70)	
Current	34	47 284	1.46 (0.89 to 2.38)	.13	31	40 638	1.37 (0.72 to 2.62)	.32
Duration of use, y								
<10	23	43 458	1.15 (0.72 to 1.82)		11	25 971	0.84 (0.38 to 1.88)	
≥10	26	27 501	1.89 (1.22 to 2.95)	.004	26	24 990	1.70 (0.87 to 3.31)	.06
Recency and duration								
Former	14	23 539	1.16 (0.65 to 2.07)		6	10 355	1.07 (0.41 to 2.78)	
Current, y								
<10	10	22 497	1.00 (0.49 to 2.03)		7	17 481	0.83 (0.33 to 2.09)	
≥10	24	24 603	1.88 (1.08 to 3.27)	.06	24	22 994	1.71 (0.87 to 3.35)	.14

*HT = hormone therapy; ET = unopposed estrogen therapy; RR = relative risk; CI = confidence interval. Among all women, recency of use was unknown for one woman who developed ovarian cancer and 992 person-years, duration of use was unknown for 857 person-years, and recency and duration were unknown for 1177 person-years. Among women with hysterectomy, recency of use was unknown for 462 person-years, duration of use was unknown for 494 person-years, and recency and duration were unknown for 625 person-years.

†Relative risks adjusted for continuous age (years), race (white, other/unknown), duration of oral contraceptive use (none, <10 years, ≥10 years, or unknown), body mass index (BMI) (<25, 25–29, ≥30 kg/m^2 or unknown), and menopause and hysterectomy (natural menopause, surgical menopause, premenopause, or unknown); models include terms for ever use of other HT formulations (ET followed by estrogen plus progestin, estrogen plus progestin only, progestin followed by estrogen plus progestin, ET and estrogen plus progestin but order unknown, other formulations, or unknown).

‡*P* values (two-sided) were calculated using Wald chi-square tests of categorical (ever use) or ordinal (recency of use and recency and duration) variables based on the categories and referent group shown. The *P* value (two-sided) for duration of use was based on an ordinal variable for total years of use at baseline (none, 1, 2, 3, …, 9, 10, or >10).

§Relative risks adjusted for continuous age (years), race (white, other/unknown), duration of oral contraceptive use (none, <10 years, ≥10 years, or unknown), and BMI (<25, 25–29, ≥30 kg/m^2 or unknown).

have an increased risk of ovarian cancer compared with never users.

Compared with women with intact uteri who never used hormone therapy, risks of ovarian cancer were higher for women taking sequential (RR = 1.94, 95% CI = 1.17 to 3.22; *P* = .01) than continuous (RR = 1.41, 95% CI = 0.90 to 2.22; *P* = .14) regimens (Table 4). Most of the women who used estrogen plus progestin and developed ovarian cancer were current users at the time of the second questionnaire. The association of ovarian cancer risk with current sequential use was stronger than that with current continuous use. For both regimens, the inconsistently elevated risks for short-duration (<5 years) use were based on few ovarian cancers, and there was no consistent duration response. Compared with no use, long-duration use (≥5 years) of sequential regimens was associated with statistically significantly increased risk (RR = 1.92, 95% CI = 1.07 to 3.46; *P* = .02; 49 versus 108 per 100 000 person-years), but long-duration use of continuous regimens was associated with statistically nonsignificantly increased risk (RR = 1.55, 95% CI = 0.97 to 2.87; *P* = .04; 49 versus 66 per 100 000 person-years; Table 4). The association with use of continuous regimens was nearly identical after excluding the women who reported 15–25 days of progestin use per cycle (data not shown).

Analyses restricted to sequential regimens containing 5.0 mg/day or 10.0 mg/day of medroxyprogesterone acetate or continuous regimens containing 2.5 mg/day or 5.0 mg/day of medroxyprogesterone acetate produced similar associations to those based on analyses of all reported sequential or continuous regimen use (RR = 3.09, 95% CI = 1.68 to 5.68; *P*<.001 and RR = 1.82, 95% CI = 1.03 to 3.23; *P* = .02, respectively) (Table 4). For both regimens, all associations restricted to these usual regimen–dose combinations were slightly stronger than the associations based on all reported estrogen plus progestin–only use, but again, no consistent duration response was observed for either regimen (Table 4).

Provera (medroxyprogesterone acetate) was the most commonly reported type of progestin. Strong overlap between usual dose and regimen limited within-regimen analyses. None of the women who reported taking continuous regimens containing 5.0 mg/day of progestin developed ovarian cancer. The relative risks associated with sequential regimens did not differ markedly by progestin dose (5.0 mg/day versus 10.0 mg/day) (data not shown).

Women who reported taking the equivalent of the common single-pill continuous combined estrogen plus progestin regimen—daily conjugated equine estrogens at 0.625 mg/day plus daily medroxyprogesterone acetate at 2.5 mg/day—accrued 16 232 person-years. Eight of these women developed ovarian cancer. The relative risk for ever use compared with never use was 1.28 (95% CI = 0.61 to 2.72).

The average reported age at first use of estrogen plus progestin was lower among sequential regimen users who developed cancer (52.1 years) and who did not (51.7 years) than among continuous regimen users who developed ovarian cancer (55.7 years) and who did not (53.9 years). Almost all the ovarian cancers among estrogen plus progestin users occurred in women who were postmenopausal and between ages 57 and 68 at baseline. Stratification by age within that range (57–60, 61–64, and 65–68 years) revealed that the associations of cancer risk with sequential estrogen plus progestin use, although statistically significant in all three groups, were highest among women aged 57–60 years and declined as age increased (data not shown). Conversely, the associations with continuous estrogen plus progestin use increased as age group increased and were statistically significant only among women aged 65–68 at baseline (data not shown). Results

Table 3. Associations between estrogen plus progestin and ovarian cancer in 73 483 women without hysterectomy at baseline*

Hormone therapy	No. of cancers	Person-years	RR† (95% CI)	P‡
No HT use	73	150 413	1.00 (referent)	
ET only	12	20 108	1.23 (0.67 to 2.27)	.51
ET and EPT	10	13 169	1.66 (0.87 to 3.24)	.13
EPT only	50	82 754	1.50 (1.03 to 2.19)	.04
Duration of EPT-only use, y				
≤1	7	13 866	1.20 (0.55 to 2.62)	
2–4	11	22 625	1.24 (0.65 to 2.39)	
5–9	13	25 647	1.30 (0.71 to 2.39)	
≥10	19	20 472	2.15 (1.28 to 3.62)	.008
Recency of EPT-only use				
Former	8	14 448	1.29 (0.62 to 2.68)	
Current, y				
<10	25	48 693	1.33 (0.82 to 2.14)	
≥10	17	18 997	2.08 (1.21 to 3.57)	.01

*HT = hormone therapy; ET = unopposed estrogen therapy; EPT = estrogen plus progestin therapy; RR = relative risk; CI = confidence interval. Other reported combinations of hormone therapy formulations included EPT and ET (1088 person-years), PT and EPT (1025 person-years), ET and PT (one cancer and 923 person-years), EPT and PT (one cancer and 732 person-years), PT and ET (680 person-years), unknown combination of estrogen and progestin (two cancers and 9984 person-years), other formulations (six cancers and 9900 person-years), and unknown HT use (257 person-years).

†Relative risks adjusted for continuous age (years), race (white, other/unknown), menopausal status (premenopausal, postmenopausal, or unknown), duration of oral contraceptive use (none, <10 years, ≥10 years, or unknown), and body mass index (BMI) (<25, 25–29, ≥30 kg/m^2 or unknown). Women who used EPT but for whom prior or subsequent ET could not be determined accounted for 15 713 person-years; five developed ovarian cancer (RR = 0.73, 95% CI = 0.30 to 1.82). Reported "other" hormone therapy formulations accounted for 9900 person-years and unknown hormone therapy accounted for 257 person-years. Duration of EPT-only use was unknown for 145 person-years, and recency and duration was unknown for 641 person-years.

‡*P* values (two-sided) were calculated using Wald chi-square tests of categorical (ever use) or ordinal (recency of EPT only) variables based on the categories and referent group shown. The *P* value (two-sided) for duration of use was based on an ordinal variable for total years of use at baseline (none, 1, 2, 3, …, 9, 10, or >10).

were similar after excluding the 8054 women who reported a previous other ovarian surgery at baseline (data not shown).

Cumulative Incidence

The cumulative incidence of developing ovarian cancer in this population was 5.5 per 10 000 person-years. Among women with a hysterectomy, unopposed estrogen users had a 28% higher cumulative incidence compared with never users (7.2 versus 5.6 per 10 000 person-years). Among women with intact uteri, the cumulative incidence for women who never used hormone therapy was 4.9 per 10 000 person-years, whereas cumulative incidence in estrogen plus progestin users (6.0 per 10 000 person-years), sequential estrogen plus progestin users (10.2 per 10 000 person-years), and continuous estrogen plus progestin users (6.6 per 10 000 person-years) were 22%, 108%, and 35% higher, respectively.

Discussion

In this large cohort, women who used menopausal hormone therapy had elevated risks of developing ovarian cancer compared with women who used no therapy. The increased risks differed by hormone therapy formulation and regimen and varied according to hysterectomy status. The changing formulations, regimens, and patterns of use since the 1970s *(22,25)* pose challenges for elucidating ovarian cancer risks, which might not emerge until well after use begins. Our relatively detailed data on substantial numbers of hormone therapy users extend the understanding of ovarian cancer by revealing increased risks for women with intact uteri who used estrogen plus progestin formulations.

The cohort's large size and recent data collection allowed us to investigate contemporary hormone therapy use, including unopposed estrogen among women with hysterectomy and estrogen plus progestin among women with intact uteri who only used this formulation. Emphasizing these patterns of use among women who reported specific regimens and doses further increased both the internal and external validity of the findings. We considered most known ovarian cancer risk factors, which reduced the potential for confounding.

The increased risks among long-duration unopposed estrogen users match what other recent US studies observed in analyses that adjusted for hysterectomy status. Three cohort studies *(5,6,8)* and one case–control study *(10)* found increased risk among 10-year users. Another cohort study (Danforth KN, Tworoger SS, Hecht J, Rosner BA, Colditz FA, Hankinson SE: personal communication) reported increased risks among women with 5 or more years of estrogen use. Risk estimates in women with hysterectomy are less consistent, but our data indicate that risk of ovarian cancer might be elevated yet slightly attenuated in women with hysterectomy who take unopposed estrogen for long durations. One cohort study found stronger associations with ovarian cancer risk among women with hysterectomy who took unopposed estrogen for a long duration than women with intact uteri *(5)*, and a case–control study reported a statistically nonsignificant positive association with more than 5 years of estrogen use *(14)*. Two other case–control studies *(9,13)* reported weak and statistically nonsignificant inverse associations with conjugated equine estrogens.

Duration of unopposed estrogen use appeared to be more important than recency of use in our study. Consistent with other studies *(5,6,10)*, we observed that most long-duration unopposed estrogen users were also current users. Millions of US women have used unopposed estrogens, but only a minority have used them for long durations *(26)*. If ovarian cancer risks decline after cessation of long-duration use but remain elevated, as seems to occur with hormone therapy–associated breast cancer risks *(27)*, then ovarian cancer risk could be a concern for long-duration users for some time after use ceases. Adherence to current recommendations, which emphasize short-duration low-dose use for menopausal symptom management only *(28,29)*, would decrease the future number of long-duration unopposed estrogen users. The populations at risk might then only include women who undergo premature surgical menopause and women whose persistent menopausal symptoms long after menopause necessitate use of unopposed estrogen for many years *(30,31)*. At present, there remain insufficient data to estimate risk after stopping unopposed estrogen therapy.

Existing US studies included primarily women who likely used at least 0.625 mg/day of conjugated equine estrogens. Even this large study of more than 97 000 women included few who used other estrogen preparations or doses. Whether estrogens taken at those doses are associated with ovarian cancer is unknown.

Table 4. Associations between use of only estrogen plus progestin and ovarian cancer in women without hysterectomy at baseline*

	All EPT-only use (N = 58 855)				EPT only at usual regimen–dose combinations† (N = 51 698)			
Hormone therapy	No. of cancers	Person-years	RR (95% CI)	P‡	No. of cancers	Person-years	RR (95% CI)	P‡
No HT use	73	150 413	1.00 (referent)		73	150 413	1.00 (referent)	
Regimen§								
Sequential	21	29 727	1.94 (1.17 to 3.22)	.01	17	16 675	2.91 (1.67 to 5.05)	<.001
Continuous	28	48 487	1.41 (0.90 to 2.22)	.14	25	37 667	1.66 (1.04 to 2.66)	.04
Regimen and recency								
Sequential								
Former	5	4825	2.58 (1.03 to 6.42)		3	1072	7.05 (2.21 to 22.5)	
Current	16	24 785	1.81 (1.03 to 3.18)	.09	14	15 553	2.57 (1.42 to 4.67)	.004
Continuous								
Former	3	7132	0.97 (0.31 to 3.10)		3	2892	2.45 (0.77 to 7.80)	
Current	25	41 039	1.51 (0.94 to 2.41)	.74	22	34 603	1.59 (0.97 to 2.61)	.25
Regimen and duration								
Sequential, y								
≤1	1	3032	0.89 (0.12 to 6.42)		1	1179	2.53 (0.35 to 18.5)	
2–4	6	7278	2.49 (1.05 to 5.90)		3	4102	2.35 (0.72 to 7.69)	
≥5	14	19 451	1.92 (1.07 to 3.46)	.02	13	11 394	3.09 (1.68 to 5.68)	<.001
Continuous, y								
≤1	6	9065	1.55 (0.67 to 3.58)		5	5844	2.06 (0.82 to 5.13)	
2–4	5	14 252	0.86 (0.34 to 2.17)		5	11 319	1.12 (0.45 to 2.82)	
≥5	17	25 141	1.55 (0.97 to 2.87)	.04	15	20 491	1.82 (1.03 to 3.23)	.02

*HT = hormone therapy; EPT = estrogen plus progestin therapy; RR = relative risk; CI = confidence interval. Relative risks adjusted for continuous age (in years), race (white, other/unknown), menopausal status (premenopausal, postmenopausal, or unknown), duration of oral contraceptive use (none, <10 years, ≥10 years, or unknown), and body mass index (BMI) (<25, 25–29, ≥30 kg/m^2 or unknown). Among all women who used EPT only, regimen was unknown for 4490 person-years and duration was unknown for 46 person-years. Among women who used EPT only at usual dose–regimen combinations, duration was unknown for 13 person-years.

†Sequential regimens with 5.0 mg/day or 10.0 mg/day medroxyprogesterone acetate or continuous regimens with 2.5 mg/day or 5.0 mg/day medroxyprogesterone acetate.

‡*P* values (two-sided) were calculated using Wald chi-square tests of categorical (regimen) or ordinal (regimen and recency) variables based on the categories and referent group shown. The *P* values (two-sided) for duration of use were based on ordinal variables for total years of use at baseline (none, 1, 2, 3, …, 9, 10, or >10), with separate variables for each regimen.

§Sequential regimens include progestin taken for less than 15 days per month. Continuous regimens include progestin taken for at least 15 days per month.

Women who used estrogen plus progestin for long durations also had statistically significantly increased risks for ovarian cancer compared with women who used no hormone therapy. This finding contradicts the null associations from our earlier study *(5)*, which included 18 ovarian cancers in women who used only estrogen plus progestin, and one case–control study *(13)*, which included 57 exposed case patients. The three other US studies that showed positive associations between ovarian cancer and menopausal hormone therapy use *(6,8,9)* collected exposure information when unopposed estrogen would have been used by most, if not all, women.

Other null associations of ovarian cancer risk with estrogen plus progestin were reported in studies that statistically adjusted for hysterectomy *(10,14)* or use of multiple formulations, including previous unopposed estrogen use *(7,11,13)*. The latter approach might produce statistically misleading results *(32)*, especially if long-duration unopposed estrogen use preceded estrogen plus progestin use. In the current and our previous *(5)* analyses, the increased risks of ovarian cancer among women who switched from unopposed estrogen to estrogen plus progestin were elevated and similar to the increased risks among unopposed estrogen users.

Our findings of higher risks of ovarian cancer in association with sequential than with continuous regimens are generally similar to results from a large Swedish case–control study *(7)*. The main analyses of that study included previous users of unopposed estrogens, but sensitivity analyses that were restricted to estrogen plus progestin–only users produced stronger associations with ovarian cancer risk for women taking sequential regimens (odds ratio = 1.98, 95% CI = 1.40 to 2.78) than women taking continuous regimens (odds ratio = 1.11, 95% CI = 0.71 to 1.74). The estrogens (estradiol and estriol) and progestins (19-nortestosterone derivatives, such as norethisterone) that are predominantly used in Europe differ from those used in the United States. Only 28 case patients and 138 control subjects in the Swedish study had used the conjugated equine estrogens and 17-hydroxyprogesterone derivatives, such as medroxyprogesterone acetate, that dominate the US market. These differences do not necessarily translate into different risk profiles for each preparation, dose, and regimen *(28,31)*, but they do hinder a direct comparison across studies *(11,33)*.

Sequential regimens and continuous regimens have been used by different groups of women. Monthly withdrawal bleeding accompanies sequential regimens, which have been reported to be used most commonly by perimenopausal and early postmenopausal women *(15)*. The convenience of continuous regimens (especially continuous combined regimens) and absence of breakthrough bleeding in most women after the first few months of use *(15)* are thought to contribute to preferential use among women who are years past menopause *(16)*. Because users of sequential regimens were slightly younger than users of continuous regimens in our study, a lower absolute risk of ovarian cancer among these younger users of sequential regimens might have generated higher relative risks for sequential regimens. However, age alone seems unlikely to account for the different relative risks because the absolute difference in age was minimal between groups, both groups of women began use in their mid-50s, we adjusted for continuous age, and other risk factor differences between regimens were negligible. Future studies of ovarian cancer risk in association with hormone therapy use should consider

both true differences between regimens and confounding by indication (e.g., by menopausal symptoms), which we could not address because we did not ascertain reasons for hormone therapy use.

Like the WHI estrogen plus progestin trial, our study population included more than 8000 estrogen plus progestin users whose mean age was 63 years at study entry *(19)*. With our slightly shorter follow-up period, too few women reported the equivalent dose–regimen combination to accurately estimate risk associated with the single-pill continuous combined estrogen plus progestin regimen. However, risks associated with 5 or more years of use of continuous regimens in our study (RR = 1.55, 95% CI = 0.97 to 2.87 and RR = 1.82, 95% CI = 1.03 to 3.23) were similar to the WHI hazard ratio after an average of 5.6 years of continuous use of combined estrogen plus progestin (hazard ratio = 1.58, 95% CI = 0.77 to 3.24).

The role of steroid hormones in ovarian carcinogenesis is unclear *(18)*. Unopposed estrogen and regimens that contain estrogen plus progestin both produce equivalent increases in circulating serum estrone *(34)*, but epidemiologic studies have not firmly linked higher circulating hormone levels with increased ovarian cancer risk *(35,36)*. Experimental studies in which exogenous hormones stimulated ovarian surface epithelium *(37)* and altered ovarian expression of estrogen and progesterone receptor subtypes *(38–40)* supply speculative mechanistic support for the associations we observed.

Study limitations affect our findings. Some analyses relied on small numbers of ovarian cancers. We lacked information on hormone therapy use after the second questionnaire, but the short follow-up period minimized potential exposure misclassification after study entry. Overall hormone therapy use increased in the United States between 1996 and 2000, and therefore, we expect that most participants who reported current use at baseline continued their hormone use during the study period. Consequently, reported duration of use at baseline would have systematically underestimated the true total duration of hormone therapy use in the population during the study period. We could not evaluate whether any cessation of or changes in use after baseline differed by exposure or ovarian cancer status. Even larger studies will be needed to address potential histology-specific associations with hormone therapy. Despite its usual detection at advanced stages, ovarian cancer has potentially recognizable symptoms *(41,42)*. However, the absence of specific symptoms decreases the chance that undetected ovarian cancers in hormone therapy users would have biased their self-reported exposures. We had no data on gynecologic surgery after baseline. Overall hysterectomy prevalence in the United States increased during the study period, with bilateral oophorectomy accompanying approximately half of those hysterectomy procedures. However, a decline in hysterectomy after age 55 years *(43)* means that only a small number of NIH–AARP study participants would be expected to have had gynecologic surgery after baseline. The baseline questionnaire, which was sent to a large and representative group of women over age 50, generated a low response, but 62% of its respondents completed the second questionnaire. Response was not associated with hysterectomy status or menopause. However, compared with nonrespondents, respondents to the second questionnaire were more likely to be older and non-Hispanic white, to report overall excellent or very good health, to report a BMI below 25 kg/m^2, to have been current and longer duration hormone therapy users, and to have attended college. We therefore expect that our results are generalizable to a similar population of women over age 50 years in the United States.

Since the late 1960s, menopausal hormone therapy use has grown, declined, expanded, narrowed, and shifted. Especially for rare outcomes with long latency periods, such as ovarian cancer, these dynamic exposures pose major challenges to accurately assessing risk. The increased ovarian cancer risks we observed among long-duration users of unopposed estrogens will likely diminish in importance if recent trends in use continue. Our study provides evidence that links use of estrogen plus progestin, especially sequential regimens, with increased ovarian cancer risk. The increased absolute risks appear to be small, and other risk–benefit considerations may dominate patients' and clinicians' decision making regarding hormone therapy. Nonetheless, these associations, if real, represent potentially avoidable risk factors for a highly fatal cancer and therefore warrant continued investigation.

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NOTES

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